

Pharmaceuticals in La Jolla, California. For purposes of the study, the researchers defined pesticide exposure as pesticide use for more than 20 days in any given year, a level they say is based on typical use of the chemicals in commercial grain farming. The allele in question activates a series of enzymes in the liver that metabolize and detoxify chemicals that enter the body. However, up to 10% of Caucasians have a mutant version of the allele, which results in no activity of this enzyme system. The hypothesis is that such people might be particularly susceptible to environmental toxicants because of their inability to detoxify chemicals.

While provocative, this study does have some important limitations. Its case-control design is less than ideal for studying risk factors in Parkinson's disease, because symptoms of the disease may change over time. Thus, some of the subjects in the no-dementia control group may later develop dementia. Another drawback is the study's reliance on self-reports from dementia patients. Yet another concern is "the absence of predictive value for either pesticide exposure or the allele taken alone," says Jean Harry, a group leader in the NIEHS Environmental Toxicology Program. Only the interaction between these variables was statistically significant. In addition, Harry notes that the study used "a crude estimate of pesticide exposure." Still, she says, the results offer interesting data for further evaluation.

Clearly, the gene-toxicant interaction still needs to be confirmed by further research, ideally a larger, prospective study of Parkinson's-related dementia. Several previous studies found an association between Parkinson's disease and pesticides, other toxicants, and rural living, but so far no specific pesticide or class of environmental toxicants has been definitively linked to the disease. "Overall, past studies support the notion that pesticide exposure is a risk factor for Parkinson's disease, but only in a subset of individuals," says Kurth. In fact, he says, "Most Parkinson's patients do not have a history of pesticide exposure, and the recognition of Parkinson's disease predates the development of these compounds." The gene-toxicant interaction is another tantalizing clue in the quest for the causes of Parkinson's disease in its various forms, but only time will tell whether it is a true clue or a red herring.



## Genetic Toolbox

As the Human Genome Project steadily rolls forward, much of the information on human chromosomes is being catalogued in digital databases such as GenBank, which now contains well over 141 million base pairs' worth of information on human DNA.

The problem facing scientists now is not so much how to gather genetic information, but rather how to take advantage of the data that have already been harvested. This is where researchers such as Harold "Skip" Garner are trying to make a difference. With the help of a Hewlett-Packard supercomputer and the World Wide Web, Garner and his colleagues at the University of Texas Southwestern Medical Center in Dallas are gathering useful information from GenBank and making it available to researchers across the globe.

Especially interesting to scientists that study genetically influenced diseases are the pieces of human DNA that tend to vary among individuals. Differences in these regions—called polymorphisms—can be telltale signs that a person carries a genetic disease or is genetically susceptible to getting a disease. Because GenBank contains many duplicate bits of DNA data that come from the same part of the same chromosome but from different individuals, analysis of the database can show where polymorphisms tend to occur.

Gleaning the locations of polymorphisms from the data in GenBank is the purpose of the Polymorphic Marker Predictions of Ubiquitous Simple Sequences, or POMPOUS, a suite of computer programs designed by Garner and his colleagues. Thus far, POMPOUS has found 13,261 polymorphic regions in the human genome. Information about these regions, including their nucleotide sequences, is available on the Garner laboratory home page at <http://pompos.swmed.edu>.

By clicking the POMPOUS link on the Garner home page and then following the link named Analysis of Your Sequence by POMPOUS Server, researchers can also make use of the supercomputer's eight processors and 0.5 gigabytes of RAM to compare their own data to GenBank. Not only will the computer find known polymorphic regions in the supplied DNA sequence (up to 32,000 bases long), it will also return a pair of primers for each. Primers are unique DNA sequences used to isolate the polymorphic region for further study. In a test of the software, POMPOUS identified 33 polymorphic regions in a part of a human chromosome implicated in breast and lung cancer. Twenty-two of these were shown to actually vary in a group of 36 cancer patients.

Other software tools for genetic researchers are also available from the Garner site. These can be accessed by following the Computational Biology link on the home page. One of these tools, GeneAlert, assists researchers who are analyzing a known sequence of DNA using the National Center for Biotechnology Information's BLAST programs. GeneAlert will automatically pare down the often exhaustive lists of matching DNA sequences returned from such a search to only those that are relevant, for instance, only those containing a certain keyword such as "human" or "carcinoma." Another software tool available at this site is SIGNAL, a program that can be downloaded and used to make comparisons between DNA and protein sequences. Other tools, including a complex and thorough gene hunting system, are planned for inclusion on the site in the future.

Another highlight of the Garner site is the information on biochips available by following the Chip Based & Nanovolume Biology link. The chips are a promising new technology for sorting DNA samples so that their nucleotide sequences can be identified.

A biochip contains an array of tiny, segregated spots, each with its own sequence of nucleotides. The nucleotide sequences on the biochip, to which the sample DNA strands bond, can be constructed by controlling the reagents and the amount of light that reaches each spot on the chip during construction. Currently, the Garner laboratory is experimenting with a light processing microchip and a reagent delivery system that will allow the researchers to build chips with up to 2 million unique spots. Such chips may be able to efficiently diagnose genetic diseases and identify medically relevant genes.